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Direct Technetium radiopharmaceuticals production using a 30MeV Cyclotron

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ABSTRACT

Background and the purpose of the study: Technetium-99m is the major radionuclide used in the world and mainly is provided by fission product. However extensive research has been conducted on the use of accelerators for production of ^{99m}Tc. This investigation reports the production of ^{99m}Tc radioisotope using cyclotrons and the preparation, quality control and biodistribution studies of four major Tc-radiopharmaceuticals.

Methods: The high purity molybdenum natural target (130 mg/cm^2) was irradiated in a Cyclone 30 accelerator using 160 μA of 25 MeV proton beam energy for 1000 μA-h. After dissolution, the technetium radionuclides were extracted using methyl ethyl ketone (MEK) followed by preparation of Tc-MIBI, Tc-DTPA, Tc-DMSA and Tc-phytate as radiopharmaceutical samples.

Results: The results of quality controls and animal biodistribution studies showed successful production of Tc radionuclides (including ^{99m}Tc) in the bombarded target and subsequent labelling of the kit with Tc.

Conclusion: The developed high power Mo target if constructed using enriched ^{100}Mo, could be a practical method for large-scale production of ^{99m}Tc and promising as an alternative to fission product ^{99}Mo-^{99m}Tc generators for local applications near cyclotron facilities.

Keywords: Radiopharmaceuticals, Targetry, Quality Control.

INTRODUCTION

^{99m}Tc for the use in nuclear medicine has been produced by indirect method by means of nuclear reactors (^{99}Mo- ^{99m}Tc generator) where ^{99}Mo is a fission product. ^{99m}Tc could also can be produced directly using proton bombardment via ^{100}Mo (p, 2n) ^{99m}Tc nuclear reaction (1).

One of the main advantages of the direct production of ^{99m}Tc using cyclotrons is its low environmental hazards and less waste management difficulties relative to fission-product method, however, due to relatively short half-life of ^{99m}Tc (6.02 hrs), the direct production method could only be used for local applications.

Many research groups have studied small scale production of ^{99m}Tc by low current proton beam bombardment of molybdenum targets in accelerators using direct and indirect methods (2-4). In most cases, molybdenum targets for ^{99m}Tc production in accelerators have been produced using thin layer coating, metallic foil preparation, molybdenum oxide precipitation and pills made from molybdenum powder and/or its compounds (5), but due to the low heat transfer characteristics of these targets, which cannot withstand high currents, the production of ^{99m}Tc in large scale have not yet been achieved (6). Successful thick metallic natural molybdenum target with high thermal conductivity to produce ^{99m}Tc using high current proton beams (7) has been reported. It should also be mentioned that the use of Mo target enriched in ^{100}Mo instead of natural Mo and the choice of the suitable proton energy, and high current will result in much higher activity of ^{99m}Tc and very low amount of impure by-products (2).

In order to investigate the performance of the designed high power molybdenum target, proton bombardment of the constructed natural molybdenum target was conducted at 160 microamperes (the highest accessible current in cyclotron under study at the time of experiments). All the above reported investigations have been carried out to find out the efficacy of our designed and constructed high power Mo target to produce ^{99m}Tc on a large scale with the capability of its labelling with Tc kits (Fig. 1.). After targetry studies, fabrication and production of

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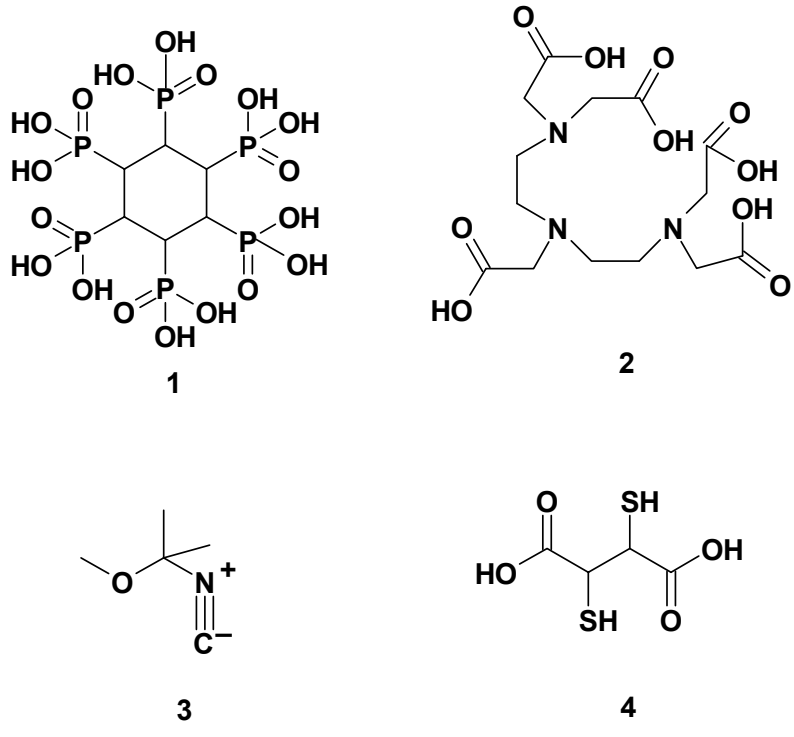

Figure 1. Structural formula for the Tc-ligands prepared in this study.

Tc radioisotopes, the sterile final TcO_4^- solution was used in radiopharmaceutical preparation followed by common quality control tests and biodistribution studies in wild-type rats.

MATERIAL AND METHODS

Instant thin layer chromatography (ITLC) was performed by counting Whatman paper using a thin layer chromatography scanner, Bioscan AR2000, Bioscan Europe Ltd. (France). All calculations and RTLC counting were based on ^{99m}Tc 140.5 keV peak. Natural molybdenum with high chemical purity (more than 99%) was obtained from Merck Chemical Co. (Germany). Tc cold kits were purchased from Kavoshyar Co. Tehran, Iran.

Targetry

The detailed targetry of the Mo target has been reported previously (7). Briefly, natural molybdenum isotopes with an approximate thickness of 130 mg/cm^2 (about 130 µm) were coated as metallic layer on copper backing on an area of 20.5 cm^2 using thermal spray coating method (8). The prepared target was irradiated by 160µA protons beam of 25 MeV for 1000µA-h in a Cyclone30). At this angle, the effective thickness of the target is about 10 times of the actual thickness (i.e. 1300mg/cm^2 approx.).

Radionuclides assays

The activities of various technetium radionuclides produced in the target were measured 12 hrs after EOB using gamma spectroscopy system with an HPGe detector of 38.5% relative efficiency. Calibration of energy and efficiency of this detector was achieved by a mixed-radionuclide (^{133}Ba, ^{241}Am, ^{137}Cs, ^{60}Co and ^{152}Eu) reference source. The detector was coupled to an MCA Plug-In Card, and the card was connected to an IBM-compatible PC-AT.

Extraction of TcO_4^- in normal saline for kit radioradiolabeling

The molybdenum target layer was rapidly dissolved by the use of a mixture of warm HNO_3 and HCl, (6.7, and 13.3 ml, respectively). After dissolution, the pH. of the mixture was changed to basic by the addition of NaOH and the radioactive TcO_4 was extracted into an equivolume of methyl ethyl ketone (MEK) (9). After four solvent extractions, the technetium bearing MEK fraction was blown dry in a nitrogen stream at 100°C and taken up in 1ml of 0.9% physiological saline. This activity (pH=7) proved to be >99% TcO_4^- as shown by thin-layer chromatography (TLC) (silica gel, MEK Rf=0.9). The TcO_4^- solution was next passed through a sterile, 0.22 µm filter (Millipore, Millex GV) prior to introduction into any commercial kit preparation.

Chemical purity control

The presence of $Cu2^+$, Zn^{2+} and MoO_4^{2-} ions were detected

in the final TcO_4 solution using simple colorimetric tests. The presence of zinc and copper cations was detected by visible colorimetric assays (10, 11).

For MoO_4^{2-} ion detection, two instant colorimetric methods were developed through some modifications in the reported method (12). Typically, equal volumes of final pharmaceutical Solution, 10% ammonium thiocyanate solutions and 5% stannous chloride (solution in diluted. HCl) were mixed. The yellow coloration as a result of $(NH_4)_3[Mo(CNS)_6]$ water soluble complex formation appeared by using blank and standard samples (limit of detection 0.1 ppm).

Preparation of [Tc]-radiopharmaceuticals

All kits were labelled at room temperature except MIBI. Typically, 20-30 mCi (about 1 GBq) of TcO_4 prepared in 1ml of 0.9% physiological saline was introduced into the commercial related kit, shaken and kept at room temperature for 30 min. At the end of labelling, radiochemical purities were verified by both standard TLCs (Whatman No.2, mobile phases of saline and silica gel using MEK as eluent).

Biodistribution of Tc-radiopharmaceuticals in wild-type rats

Each Tc-tracer was administered to three separate normal rat groups. A volume (50 µl) of Tc-tracer solutions containing 80±2 µCi radioactivity was injected intravenously to rats via their tail veins. The animals were sacrificed at exact time intervals (30, 60 and 120 min), and the ID/g% of different organs was determined as percentage of injected dose (based on the area under the curve of 140.5 keV ^{99m}Tc gamma line) per gram by gamma spectroscopy using HPGe detector.

DISCUSSION

Production

Extraction of technetium radionuclides were successfully performed from the bombarded molybdenum target at the specific pH with the lowest impurities and timely manner. Due to the use of natural Mo target, several technetium radioisotopes were produced as by-products of ^{99m}Tc such as ^{99m}Tc (6.02 hrs), ^{96}Tc (104.4 hrs), ^{95m}Tc (1464 hrs), ^{95}Tc (20.0 hrs), ^{94}Tc (4.8 hrs) and ^{93}Tc (2.75 hrs). The chemical purity of the final solution was checked by colorimetric method. The data for 5 different runs are summarized in Table 1.

Radionuclidic studies

The γ-ray spectrum of the diluted sample of Tc radionuclides 12 hrs after the end of bombardment (EOB) has been reported previously (7).

According to the results of investigations carried out by Lagunas-Solar (2), it is anticipated that using enriched ^{100}Mo instead of ^{nat}Mo and proton beam of about 1mA, about 100 Ci of ^{99m}Tc could be produced. However, 100% enriched ^{100}Mo is not available, so reactions leading to the formation of radionuclide impurities such as ^{94}Tc, ^{95}Tc and ^{96}Tc are of high concern for the production of high purity ^{99m}Tc from enriched ^{100}Mo targets. Recently, Cross-sections for the proton induced reactions on natural molybdenum was measured in the proton energy range 8.4-37.1 MeV in order to monitor the presence of other technetium nuclides better (13).

Radiolabeling procedures

After extraction of TcO_4^- in normal saline for kit radioradiolabeling, preparation of [^{99m}Tc]-complexes as model radiolabeled kits was investigated. Four major Tc-cold kits were considered as models for the feasibility study of final radionuclide labelling performance.

At the end of labelling, radiochemical purity in excess of 97% was shown by both standard TLCs (Table 2).

Biodistribution studies

Figure 2. shows the biodistribution of Tc-DTPA as a kidney perfusion agent, this water soluble complex is washed out from the kidneys and finally accumulates in bladder especially after 60 min post-injection. A small portion of the activity is also present in the stomach and lung. Thyroid uptake is negligible (about 0.01%), demonstrating the absence of free pertechnetate.

Figure 3 shows the biodistribution of Tc-MIBI in the rat organs, being used mostly as a tracer in SPECT cardiology. MIBI was selected as another model kit. As expected in 30 min post injection the major target organ is myocardium, while kidney, faeces and stomach are also major accumulation sites. Again, thyroid uptake is low in all time intervals.

Another Tc-kit used in this study was phytate, a poly phosphate compound, easily radiolabled by Tc. The final complex is mainly accumulated in reticuloendothelial system, including the liver, a major site of accumulation, and then with less contents in the spleen and the lung respectively. Negligible thyroid uptake is observed (Fig4.).

Finally Tc-DMSA was another selective kidney tracer which was radiolabeled in this study in order to demonstrate the purity and labelling capacity of Tc produced in this work. Figure 5. demonstrates that the complex is washed out from the kidneys and finally accumulates in bladder specially after 60 min post-injection. Thyroid uptake is negligible (about 0.02%), demonstrating the absence of free pertechnetate.

The results of measurements are in agreement with the expected time behaviour of the kit in different organs (14, 15), which shows the successful production of Tc radionuclides (including ^{99m}Tc) in the bombarded target and subsequent labelling of the kit with Tc.

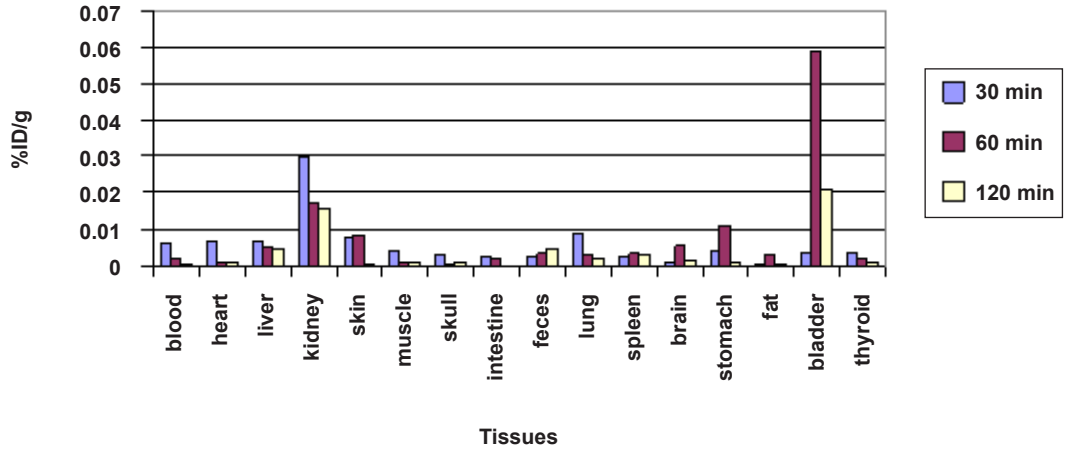

Figure 2. Calculated ID/gr% of TcDTPA (80 μCi), 30-120 minutes post I.V. injection in wild-type rat organs.

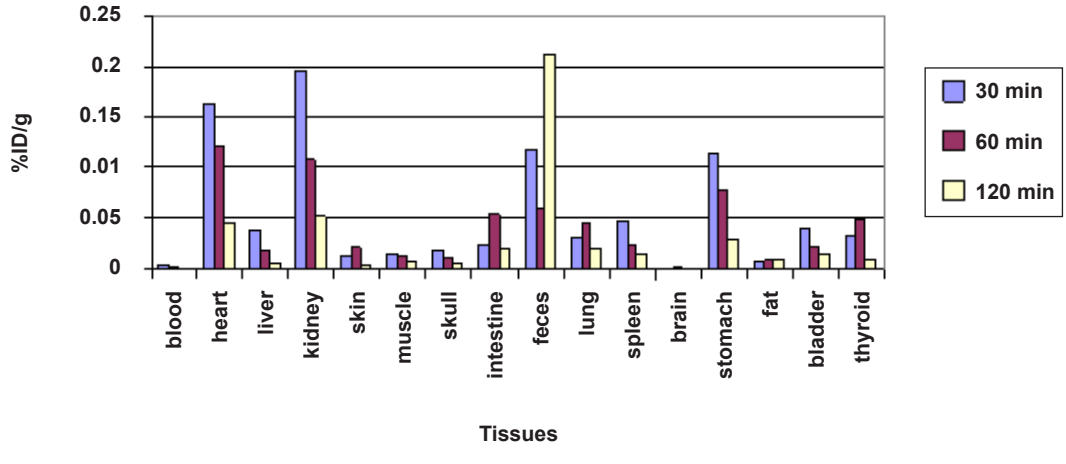

Figure 3. Calculated ID/gr% of Tc-MIBI (80 μCi), 30-120 minutes post I.V. injection in wild-type rat organs.

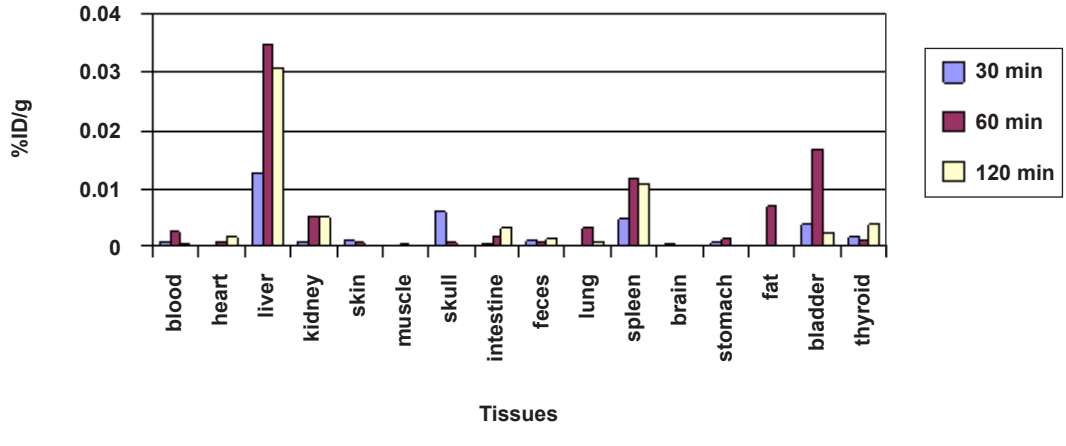

Figure 4. Calculated ID/gr% of Tc-phytate (80 μCi), 30-120 minutes post I.V. injection in wild-type rat organs.

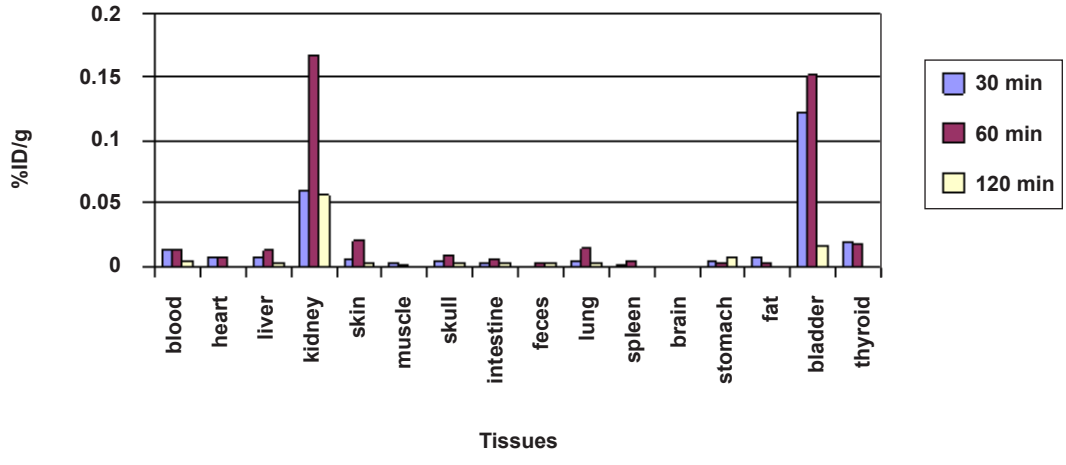

Figure 5. Calculated ID/gr% of Tc-DMSA (80 μCi), 30-120 minutes post I.V. injection in wild-type rat organs.

Table 1. Colorimetric data for 4 different sample runs.

Ion species	Reagent	Color	Run 1	Run 2	Run 3	Run 4
Cu^{2+}	Dithisone	*Pinkish*	*<1 ppm*	*<0.5 ppm*	*<1 ppm*	*<0.5 ppm*
MoO_4^{2-}	NH_4SCN, Sn^{2+}	*Yellow*	*<0.2 ppm*	*<0.1 ppm*	*<0.1 ppm*	*<0.1 ppm*
Zn^{2+}	Dithisone	*Purple*	*<0.2 ppm*	*<0.1 ppm*	*<0.2 ppm*	*<0.3 ppm*

Table 2. ITLC systems used for the radiochemical purity of the Tc-complexes on Whatman No. 2 papers.

solvent	TcO_4	Tc-radiopharmaceutical	colloids
MEK	0.9	0.2-0.1	0.0-0.1
Normal saline	0.8	0.1	0.05
saline/acetone	0.5	0.0	0.05

Table 3. Radioradiolabeling properties of four Tc-kits used in this study.

Compound	Labelling time (min)	Radiochemical purity (%)	R_f in MEK	Temperature (ºC)
Tc-DMSA	5	97±2	0.1	25
Tc-MIBI	20	94±3	0.05	90
Tc-DTPA	5	98±1	0.0	25
Tc-Phytate	10	96±2	0.1	25

The radiopharmaceutical were administered to normal rats and showed acceptable ID/g % as a Tc-radiopharmaceutical. This observations show the production of Tc radionuclides (including ^{99m}Tc) and subsequent successful labelling of the kit. It is also anticipated that the developed coating method for production of high power Mo targets using enriched ^{100}Mo instead of natural Mo, is capable to produce about 100 Ci of ^{99m}Tc using proton beam of about 1mA.

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